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**EFFECTS OF
DEXTROMETHAMPHETAMINE ON
SUBJECTIVE FATIGUE**

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13. ABSTRACT (Maximum 200 words) Declining aircrew performance during periods of sustained flight operations (SUSOPs) has underscored the need to develop effective countermeasures. This paper reports on the ability of the central nervous system (CNS) stimulant d-methamphetamine to alleviate the detrimental effects of a simulated SUSOPs on subjective fatigue. Subjective fatigue was repeatedly measured by three questionnaires. The simulated SUSOP started at 1800 and consisted of a 9-h planning session followed by 4 h of rest and a 14-h mission. After 6 h of sleep, the 9/4/14 work/rest/work pattern was repeated. At 4 1/2 h into the second mission, 13 subjects were administered 10 mg of d-methamphetamine/70 kg of body mass while 12 subjects received a placebo in a double-blind procedure. Administration of d-methamphetamine significantly reduced reported fatigue scores on the Addiction Research Center Inventory (ARCI), Mood Questionnaire (MQ), and sleepiness scores on the Stanford Sleepiness Scale (SSS).				
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SUMMARY PAGE

THE PROBLEM

Carrier flight operations often involve repeated, extended missions that are separated by short periods of rest. When these factors combine with high cockpit workload and the stress of combat, aircrew performance may become impaired. Several countermeasures, including the use of pharmacological intervention, have been proposed to alleviate the detrimental effects of sustained flight operations (SUSOPs). For example, one solution is to introduce a short-acting stimulant that could alleviate the impact of SUSOPs, delay performance decrement, and reduce subjective feelings of fatigue with minimal central nervous system (CNS) side effects. Amphetamines, have shown promise in counteracting some of the performance decrements and subjective fatigue associated with SUSOPs, but more research is needed.

FINDINGS

Following a simulated SUSOP scenario where subjects were administered either 10 mg of d-methamphetamine/70 kg of body mass, or a placebo, differences in fatigue and sleepiness were found between the methamphetamine and placebo groups. Results indicated that the administration of 10 mg of d-methamphetamine/70 kg of body mass significantly decreased subjective feelings of fatigue.

CONCLUSIONS

The amphetamines have been shown to abate subjective fatigue and improve degraded performance, however, this may not be sufficient evidence to recommend their use at this time. Several important operational considerations need to be addressed before recommendations could be proposed to the fleet. These issues include, but are not limited to:

1. Whether stimulants are the best solution to the SUSOPs problem?
2. Which stimulant is the best choice for use during SUSOPs?
3. What is the effect of the drug on flight performance?
4. What is the most efficacious dose, and how frequently could this be safely repeated during a mission?
5. When is the optimum time to use the drug during a mission?
6. What is the effect of the drug on sleep latency and how will this impact subsequent crew rest following its use during a mission?
7. What constitutes a practical and effective screening program?

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INTRODUCTION

Naval aircrews frequently fly multiple extended missions separated by brief periods of crew rest. As such, sustained flight operations (SUSOPs) can have a disruptive effect on routine sleep patterns. These disruptions often take the form of partial sleep loss, disruption of sleep-wakefulness cycles, and circadian desynchronization. Any one or more of these factors may combine with high-workload schedules to impair aircrew performance (1).

Several countermeasures have been proposed to alleviate the detrimental effects of SUSOPs on aircrews (2). Some that have been proposed include adequate squadron staffing, cross-training aircrews to enable one crew member to relieve another, and work/rest scheduling which reflects disruptions of circadian rhythm (3). Other less obvious countermeasures that may be considered include physical fitness and exercise (4), nutrition (5), and sleep strategies (6). In addition, pharmacological intervention may hold some promise.

Two classes of pharmacological countermeasures have received attention: hypnotics and stimulants. Hypnotics could increase the quality of sleep when the opportunity for sleep arises (7). The optimal hypnotic agent would decrease sleep latency, preserve normal sleep architecture, and exhibit no residual effects. Recent attention has focused on the use of benzodiazepines. Although clinically tested, more applied research is needed to warrant their use in the fleet.

Stimulants have been effective in countering the effects of SUSOPs (8,9). For example, caffeine enhances performance (10,11) and alleviates the effects of sleep loss (12) although the duration and magnitude of its effects are less than other stimulants (13). Other disadvantages of caffeine at doses likely to be useful in counteracting fatigue (> 200 mg) include tolerance, anxiety, tremor, and dysphoria (11,14). Several other stimulants such as magnesium pemoline, methylphenidate, ephedrine, phenmetrazine, pipradol, and phendamine have demonstrable effects on performance as well (15,16). They also possess undesirable side effects, however, that limit their use by aircrews (10,16).

We desired a short acting stimulant with minimal central nervous system (CNS) side effects that was known to delay performance decrements and counteract mood changes related to SUSOPs. The amphetamines, particularly d-amphetamine, have been successful in counteracting some performance decrements and mood changes associated with SUSOPs (8,9,17). Weiner (18) found that methamphetamine demonstrated greater CNS potency with less peripheral cardiovascular side effects than racemic amphetamine, while Martin et al. (16) found no differences in physiological, subjective, or behavioral effects between d-amphetamine and d-methamphetamine. Brown et al. (19) found the elimination half-life for d-amphetamine to be approximately 6-7 h, while the biological half-life for methamphetamine has been reported in the range of 4-5 h (20). Given these considerations, we chose to conduct our study using d-methamphetamine.

Aircrews who continually perceive themselves as highly fatigued may eventually show a loss in morale, which adversely affects operational effectiveness. Therefore, an important part of this research has been to evaluate subjective fatigue during SUSOPs. Although several questionnaires effectively measure subjective fatigue and sleepiness, not all of them can differentiate between drug and placebo effects. As a result, we selected instruments from three specialty areas: the Addiction Research Center Inventory (ARCI) from the pharmacological literature (21) the Mood Questionnaire (MQ) from the psychiatric literature (22), and the Stanford Sleepiness Scale (SSS) from the sleep literature (23,24).

METHODS

SUBJECTS

Twenty-five male U.S. Marines, 22-28 years old, volunteered for the study. Subjects were awaiting assignment to primary flight training. All subjects were commissioned officers who had completed a college degree program. Before participation, each subject passed a flight physical and was screened for drug use.

APPARATUS

Tests were presented using Zenith Z-248 microcomputers equipped as described in a related paper (25). The six work stations were linked by a Local Area Network (LAN) to ensure the simultaneous presentation of the tasks.

TRAINING

Subjects trained for 6 days beginning on a Monday. The final training session was conducted on the following Monday to counteract any loss of training over the weekend. Subjects completed 5 administrations of the ARCL, and 10 administrations of the MQ and SSS for familiarization before the experiment.

EXPERIMENTAL DESIGN

The experimental design is shown in Fig. 1. As in a similar study (25) the simulated SUSOP consisted of 9 h of preflight planning (Planning I), 4 h of rest, and a 14-h mission (Mission I). To simulate cyclical operations, two iterations of the preceding schedule were incorporated in the experiment, separated by a 6-h rest period. The planning and mission segments during the second cycle are labeled Planning II and Mission II in Fig. 1. Subjects were continuously monitored to ensure that they did not fall asleep during the study. Four hours and 20 min into the second mission (50 h and 40 min from the onset of the SUSOP), 13 subjects were administered 10 mg of d-methamphetamine hydrochloride/70 kg of body mass (Arenol Chemical Corp.) while 12 subjects received a placebo (lactose), following a double-blind procedure. Both the placebo and d-methamphetamine were administered in No. 0 gelatin capsules (Eli Lilly & Co.). Lactose powder was added to the appropriate dose of d-methamphetamine to fill the capsules.

The testing environment was strictly controlled. Social interaction was limited to the minimum necessary to conduct the study. The windows in the testing room were covered, and no watches or clocks were permitted in the testing areas to reduce time-of-day cues. Dietary intake was limited to 3100 cal per day. Nicotine products were prohibited as well as beverages containing methyl-xanthines.

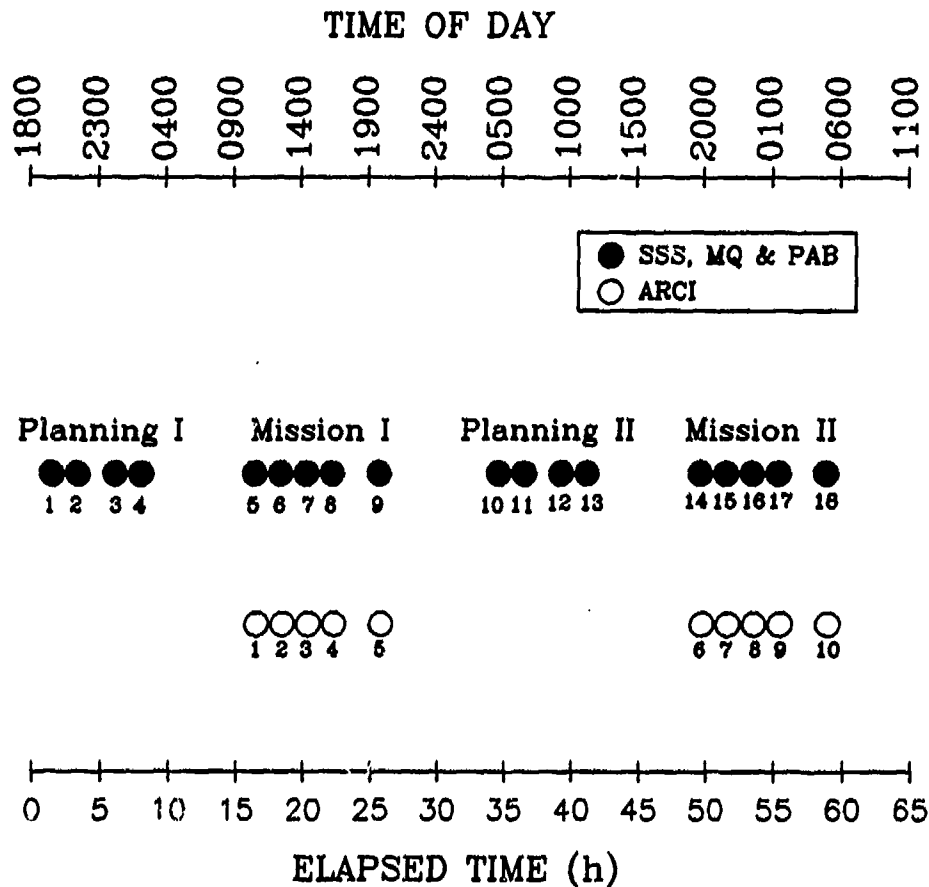


Figure 1. *Schedule for simulated sustained flight operations (SUSOPs) scenario.*
Each symbol represents a separate test administration. Pill administration (not shown) occurred at 2040 on day 3 (50 h 40 min elapsed time).

MEASURES

The ARCI, SSS, and MQ were part of a group of subjective, cognitive and physiological measures used during a the study. Although the ARCI and MQ are each comprised of several scales, each contains a fatigue scale. We restricted our analysis to the fatigue scales because we were primarily interested in fatigue during SUSOPs. A computerized flight simulator was used to occupy the subjects' time between sessions 8 and 9 during Mission I, and sessions 17 and 18 during Mission II. A generic performance assessment battery (G-PAB) was periodically administered to measure cognitive performance. The cognitive test results are reported separately (25,26). In addition, several physiological measurements, including heart rate, blood pressure, grip strength, electrocardiogram, electroencephalogram and urine output were collected for future analysis. All subjective questionnaires and cognitive tasks were computerized and presented to the subjects on a CRT screen for ease of administration. Responses for the ARCI and the flight simulator were made using a standard computer keyboard, while responses for the MQ and SSS were made using the Mini-Modulus III keypad.

Addiction Research Center Inventory (ARCI)

The ARCI used in this study was a subset of the one originally developed by Heartzen (21) and later expanded by Martin et al. (16). The ARCI was designed specifically to 1) distinguish between drug and placebo conditions, 2) determine dose-effect relationships, and 3) distinguish between different drugs. We used 5 of the 10 original scales: PCAG (pentobarbital, chlorpromazine, and alcohol group), MBG (morphine-amphetamine group), LSD (lysergic acid diethylamide), A (amphetamine), and BG (amphetamine group). The PCAG scale is a measure of fatigue, the MBG scale represents euphoria, the LSD scale is an indication of depersonalization, and the A and BG scales are both measurements of intellectual efficiency. The scales that were not included apply to pharmacological agents other than amphetamine. What makes the ARCI particularly appealing is its successful use in the investigation of subjective and behavioral effects of amphetamines (16,27).

During each trial, a statement was displayed to the subject. Subjects were instructed to answer "true" if the statement applied to them at that time and "false" if it did not. A total of 47 statements from the 5 selected scales were combined and displayed randomly during each session. Fifteen of the 47 statements presented during each session were associated with the fatigue scale (see Appendix A for ARCI fatigue scale statements). Scores could range from 0 (no fatigue) to 15 (maximum fatigue).

Stanford Sleepiness Scale (SSS)

The SSS is a self-rating scale used to quantify progressive steps in sleepiness developed by Hoddes et al. (23,24) in an effort to correlate subjective sleepiness ratings with performance. During each session, seven items were simultaneously presented to the subjects. Subjects were instructed to enter the scale value of the statement that best described their state of sleepiness (see Appendix B for the SSS statements and their scale values). Scale values could range from 1 (wide awake and alert) to 7 (ready to fall asleep).

Mood Questionnaire (MQ)

The MQ was developed by Ryman et al. (22) as an abbreviated test to measure the moods and emotions of individuals in a form that was more amenable to field research. The questionnaire, which consists of six scales including happiness, activity, depression, fear, anger, and fatigue, has been validated using several objective performance criteria (28-30).

During each trial, an adjective was presented to the subject. Subjects were instructed to indicate how each word applied to them by using a three-choice response format (1 = not at all, 2 = somewhat or slightly, 3 = mostly or generally). During each session, 36 adjectives from the 6 scales were randomly displayed. Five of the 36 adjectives comprised the Fatigue scale (see Appendix C for MQ fatigue scale adjectives). Scores could range from 5 (no fatigue) to 15 (generally fatigued).

The SSS and MQ were administered 18 times during the testing period as part of a larger study, as illustrated in Fig. 1. There were four administrations during each planning session and five during each mission session. The ARCI was administered 10 times during the testing period. There were five administrations during each mission segment, with no administrations during the planning segments.

RESULTS

We found no differences in reported fatigue/sleepiness between the methamphetamine and placebo groups before pill administration for any of the questionnaires. Differences in fatigue and sleepiness between the methamphetamine and placebo groups for each administration during Mission II were examined using planned comparisons in a group-by-repeated measures design. A significance level of $p < .05$ was adopted for all comparisons. All three subjective inventories showed significantly less fatigue in the drug group following the administration of methamphetamine.

The methamphetamine group reported significantly less fatigue than the placebo group on the ARCI at 1 h, $F(1, 23) = 11.63, p < .01$; 2 h 55 min, $F(1, 23) = 4.25, p < .05$; and 4 h 50 min, $F(1, 23) = 4.31, p < .05$, following pill administration (2140 and 2335 on day 3, and 0130 on day 4), as illustrated in Fig 2. At 8 h 20 min post pill (0500 on day 4), reported fatigue was not different between the two groups.

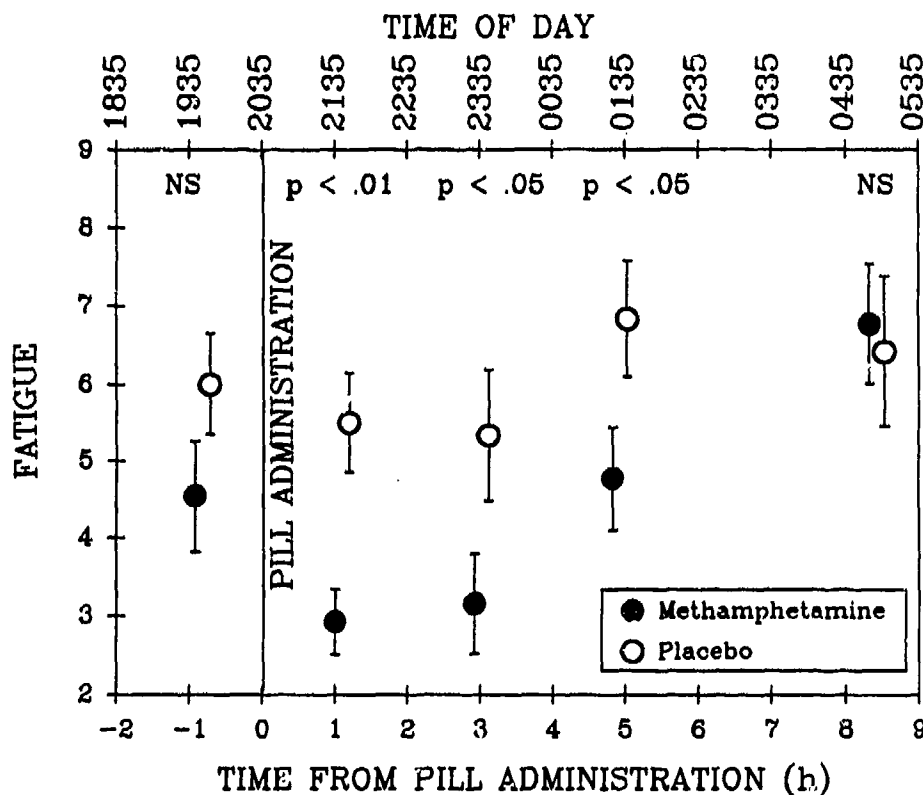


Figure 2. Subjective fatigue as a function of time for the Addiction Research Center Inventory (ARCI). Fatigue scores could range from 0 (no fatigue) to 15 (maximum fatigue). (See Appendix A for ARCI fatigue scale statements).

Mean sleepiness scores ranged from 2 ("functioning at a high level") to 3.5 (between "not at full alertness" and "a little foggy") as illustrated in Fig. 3. There were no differences in reported sleepiness between the drug and placebo groups 1 h before pill administration and 55 min after pill administration

(1940 and 2135 on day 3). At 2 h 50 min post pill (2330 on day 3), the methamphetamine group reported less sleepiness than the placebo group, $F(1, 23) = 3.99, p < .05$. At that time, the mean scores were 2 ("functioning at a high level") for the methamphetamine group and 2.75 (between "able to concentrate but not at peak" and "not fully alert") for the placebo group. For the remainder of the study, at 4 h 45 min and 8 h 15 min post pill (0125 and 0455 on day 4), reported sleepiness was essentially the same for the two groups.

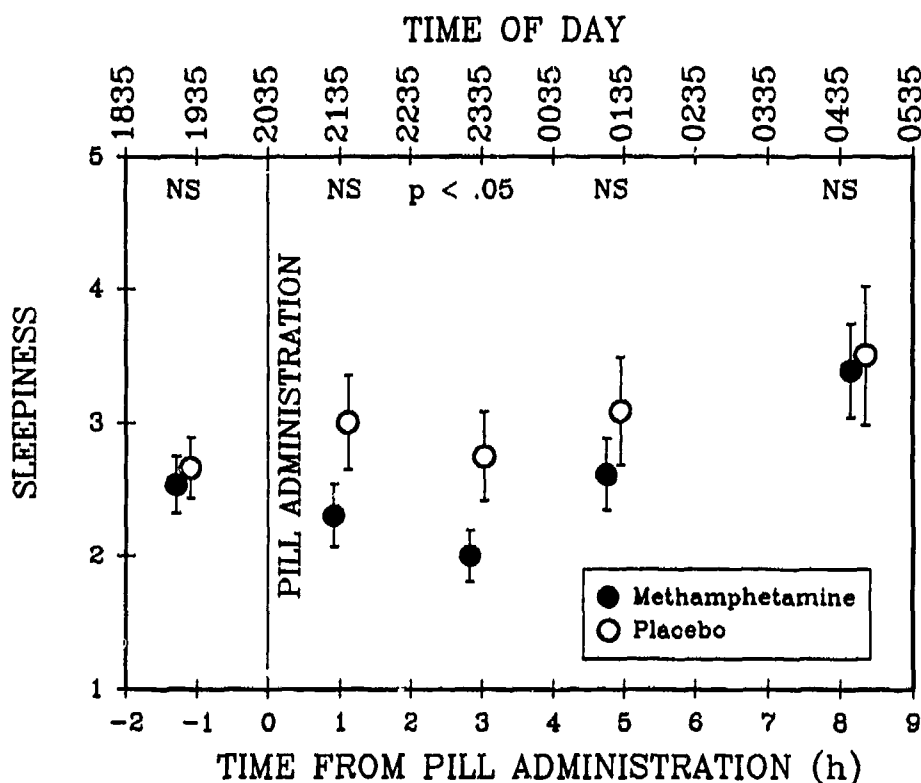


Figure 3. Subjective fatigue as a function of time for the Stanford Sleepiness Scale (SSS). Scores could range from 1 (wide awake and alert) to 7 (ready to fall asleep). (See Appendix B for SSS statements and their scale values).

The mean subjective fatigue scores for the MQ were between 6.7 and 9 (Fig. 4). There were no differences in reported fatigue between the drug and placebo groups 1 h prior to pill administration, 50 min post pill administration, and 2 h 50 min post pill administration (1940, 2135, and 2330 on day 3). At 4 h 45 min and 8 h 15 min post pill (0125 and 0455 on day 4), the methamphetamine group reported less fatigue than the placebo group, $F(1, 23) = 4.49$ and 4.26 , respectively, $p < .05$. During this period, the level of fatigue reported by both groups appeared to increase.

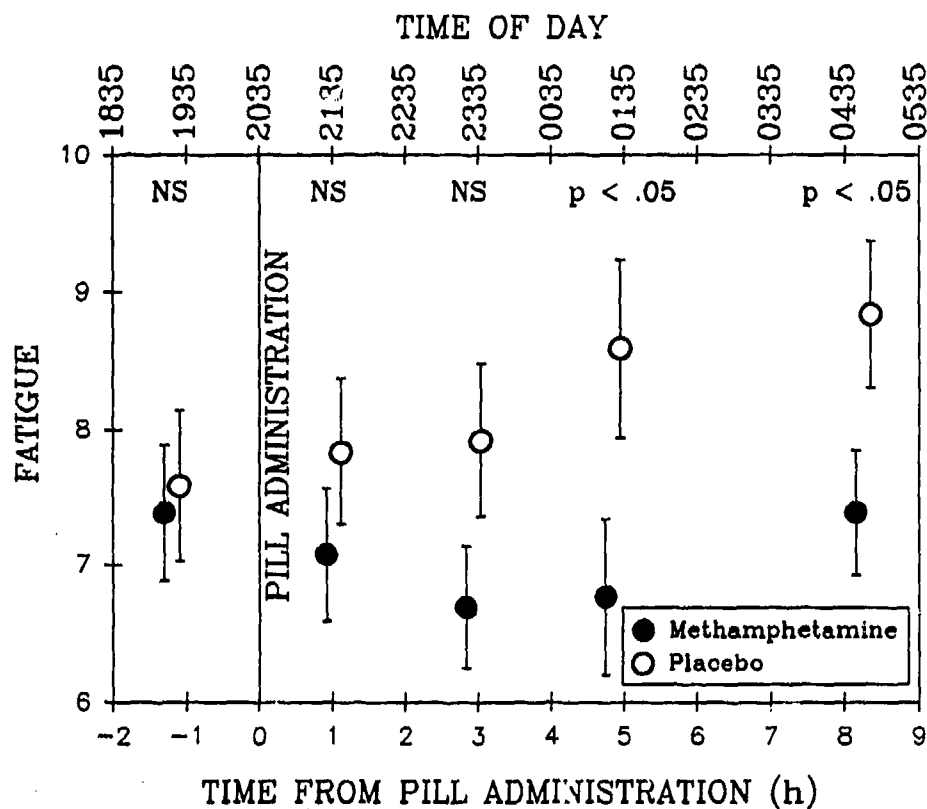


Figure 4. Schedule for simulated sustained flight operations (SUSOPs) scenario. Scores could range from 5 (no fatigue) to 15 (generally fatigued). (See Appendix C for MQ fatigue scale adjectives).

DISCUSSION

Methamphetamine administration significantly affected the results obtained from the subjective questionnaires. Fatigue tended to decrease during the simulated SUSOP with the administration of 10 mg of methamphetamine/70 kg of body mass although the reported fatigue was low for all of the questionnaires. Consistent with other findings (13,31,32) significant differences in apparent fatigue and sleepiness were found between the treatment and placebo groups following pill administration.

Fatigue reported by the drug group increased at 0130 and 0430 for the ARCI and the SSS (Figs. 2 and 3, respectively). This may have been a time-of-day effect. Endogenous circadian rhythms have been established for many physiological, biochemical, and psychological functions. Performance on many tasks rises to a peak between 1200 and 2100 and falls to a minimum between 0200 and 0600 (1). The increase in reported fatigue between 0130 and 0430 falls roughly within the 0200-0600 circadian trough. Our results are consistent with the findings of Angus and Heslegrave (33) in which performance between 0200 and 0600 declined from 10 to 15% in non-sleep-deprived individuals to as much as 35 to 40% in sleep-deprived subjects. These performance decrements were accompanied by declines in mood, motivation, and initiative. Other researchers (34,35) have found similar lulls in mood and performance during these times as well.

Figure 3 suggests that reported sleepiness increased during this period (between 0130 and 0430), indicating that the subjects may have felt sleepy as well as fatigued.

At times closer to pill administration (1 h 00 min, 2 h 55 min, and 4 h 50 min), the ARCI seemed to detect differences between the methamphetamine and placebo subjects better than the MQ. Later (8 h 15 min), the MQ appeared to be a better measure of subjective fatigue. The methamphetamine group reported less fatigue than the placebo group on the final administration of the MQ. This was not the case for the ARCI data. Although we cannot entirely explain the differences between the scales at the final administration time, they may be due to the metabolism of methamphetamine to amphetamine that is known to occur (36). It has been proposed that this active metabolite might result in the prolonged effect of methamphetamine on cognitive performance (26). It is equally possible that the metabolism of methamphetamine to amphetamine has a similar prolonged effect on subjective fatigue that the ARCI and SSS were unable to detect. Our data thus demonstrate the need to use caution when selecting subjective fatigue scales. This study suggests that the ARCI was the most effective at discriminating fatigue while the SSS was the least discriminative. When information is not available on which particular scale will be the most useful in a study, we recommend using more than one scale until sufficient data are obtained to make a decision.

Two factors might have enhanced the effect of methamphetamine on subjective fatigue. First, a higher dose of methamphetamine might have produced a greater effect. The parent compound, d-amphetamine, has been shown to ameliorate fatigue in a dose-response fashion (8). The dose of methamphetamine used in this study was low compared to the dose used in other studies. For example, dosages of d-amphetamine as high as 35 mg/70 kg of body mass have been used to study drug-induced physiological and behavioral changes in man (37). In addition, clinical doses of methamphetamine of up to 30 mg per day are common for the treatment of hyperactivity in children and obesity in adults (18). A second factor that might enhance the effect of methamphetamine involves the fatigue level of the subjects. Subjects in this study may have experienced only mild fatigue following the 60-h partial sleep-deprivation schedule. Other studies have used total, rather than partial, sleep-deprivation paradigms, and longer sleep-deprivation periods ranging from 60 h (8) to 98 h (38). Reported fatigue levels in our study were only moderate, allowing less of a chance for methamphetamine to reduce subjective fatigue. It is possible that the effect of methamphetamine might have been greater if the subjects had been more fatigued. Future research should be directed toward testing higher doses of methamphetamine under conditions of greater fatigue to allow for a full range of effects.

In this paper, we used subjective scales to evaluate the effect of d-methamphetamine on subjective fatigue. In a previous paper (26) we used cognitive tasks to investigate the effect of d-methamphetamine on performance. We compared the number of subjective scales showing significant differences between the drug and placebo groups to the number of cognitive tasks showing significant group differences at each test administration. We found that the pattern of differences between drug and placebo subjects is similar for the subjective scales and the cognitive tasks. Fewer differences were observed on subjective scales and cognitive tasks at administrations 1 and 4, when serum drug levels would have been minimal, than at administrations 2 and 3, when serum drug levels, and their effect on fatigue and performance, would have been greater. Although this is not a rigorous statistical treatment, it reveals a similarity in the way subjective indices of fatigue and cognitive measures of performance vary with test administration times.

CONCLUSIONS

Amphetamine has been shown to abate subjective feelings of fatigue in this and other studies (8,32) and to improve performance (8,13,26), however, this may not be sufficient to recommend its use in the fleet at this time. Several important operational considerations remain unanswered. Additional research is needed to determine: 1) whether stimulants are the best solution to the SUSOPs problem, 2) which stimulant would be the best choice for use during SUSOPs, 3) the effect of amphetamine on flight performance, 4) the most efficacious dose, 5) the optimum point in a mission to introduce the stimulant, 6) the effect on sleep latency and impact on crew rest, and 7) what constitutes a practical but effective medical screening program for aircrews in order to identify individuals who might have an adverse reaction to the drug.

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- Shappell, S.A., Neri, D.F., and DeJohn, C.A., "Simulated Sustained Flight Operations and Performance, Part 2: Effects of Dextro-methamphetamine." *Military Psychology*, (in press)

APPENDIX A

This appendix contains a list of the statements presented during the administration of the Addiction Research Center Inventory. The subject responded by circling each item that applied to them at the time. For statements 1-12, a point was added to the total for each item that was circled. For statements 13-15, 1 point was added to the total for each item that was not circled. Scores could range from 0 (no fatigue) to 15 (maximum fatigue).

- 1 - My speech is slurred ¹
- 2 - I am not as active as usual ¹
- 3 - I have a feeling of just dragging along rather than coasting ¹
- 4 - I feel sluggish ¹
- 5 - My head feels heavy ¹
- 6 - I feel like avoiding people although I usually do not feel this way ¹
- 7 - I feel dizzy ¹
- 8 - It seems harder than usual to move around ¹
- 9 - I am moody ¹
- 10 - People might say that I am a little dull right now ¹
- 11 - I feel drowsy ¹
- 12 - I am full of energy ²
- 13 - I can completely appreciate what others are saying when I am in this mood ²
- 14 - I feel more clear headed than dreamy ²
- 15 - A thrill has gone through me one or more times since I started answering these questions ²

¹ Statement required a true response to contribute to fatigue score.

² Statement required a false response to contribute to fatigue score.

APPENDIX B

This appendix contains a list of the statements presented during the administration of the Stanford Sleepiness Scale. Subjects were instructed to circle the one statement that applied to them at the time. This statement was their score. Scores could range from 1 (least sleepiness) to 7 (most sleepiness).

Scale	Statements
Values	
1	Feeling active and vital; alert; wide awake.
2	Functioning at a high level, but not at peak; able to concentrate.
3	Relaxed; awake; not at full alertness; responsive.
4	A little foggy; not at peak; let down.
5	Fogginess; beginning to lose interest in remaining awake; slowed down.
6	Sleepiness; prefer to be lying down; fighting sleep; woozy.
7	Almost in reverie; sleep onset soon; lost struggle to remain awake.

APPENDIX C

This appendix contains a list of adjectives presented during the Mood Questionnaire. Subjects were instructed to circle how strongly each adjective described their level of fatigue at that time by circling the number "1," "2," or "3" corresponding to "not at all," "somewhat or slightly," or "mostly or generally," respectively. The total score was calculated by adding the numbers circled. Scores could range from 5 (least fatigued) to 15 (most fatigued).

	Not at all	Somewhat or slightly	Mostly or generally
weary	1	2	3
lazy	1	2	3
drowsy	1	2	3
sluggish	1	2	3
inactive	1	2	3